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Enantioselective Acetalization of Racemic 1,3-Alkanediols with *l*-Menthone under Kinetically Controlled Conditions

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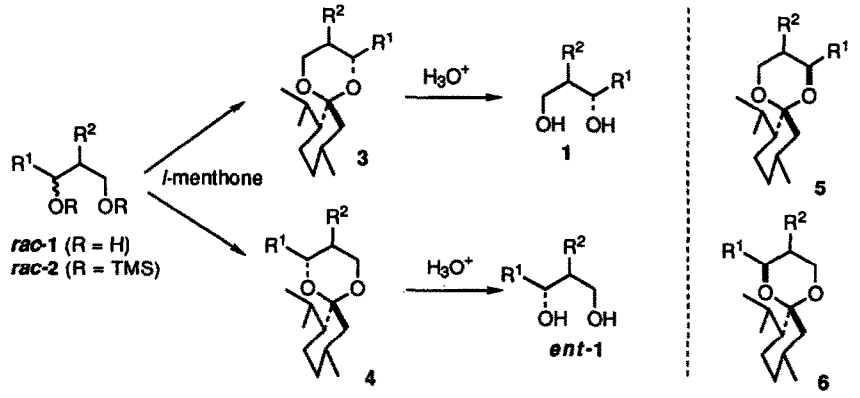
Abstract: Racemic 1,3-alkanediols (***rac*-1**) undergo an enantioselective acetalization by treatment with *l*-menthone enol trimethylsilyl ether (**10**) in the presence of trifluoromethanesulfonic acid (10 mol%) to give thermodynamically less stable spiroacetal **3** (derived from **1**) in preference to spiroacetal **4** (derived from ***ent*-1**). The kinetically controlled acetalization is applied to a novel kinetic resolution of racemic 1,3-alkanediols: Optically active diols ***ent*-1** of 55-95 % ee are obtained when the racemic diols are allowed to react with 1.5 equiv of enol silyl ether **10** under similar conditions.

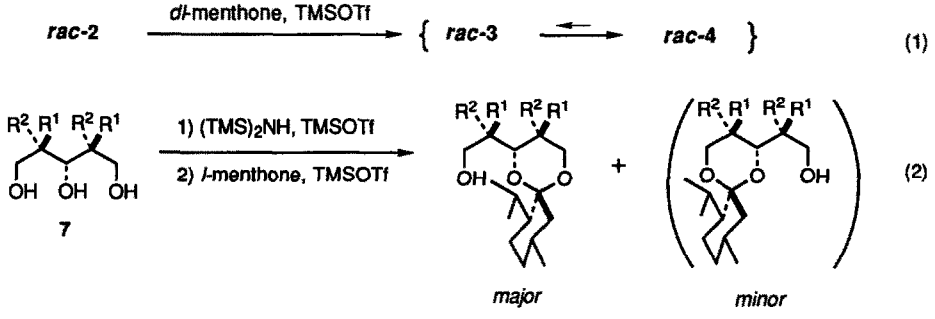
Enantiomerically pure 1,3-alkanediols and derivatives thereof are versatile chiral building blocks.[1] We recently developed an efficient and reliable method for obtaining the enantiomerically pure 1,3-diols by using *l*-menthone as chiral template (Scheme 1).[2] Acetalization of racemic 1,3-alkanediols (***rac*-1**) with *l*-menthone, via their bis-TMS ether derivatives (***rac*-2**), proceeds in a highly stereocontrolled manner at the resulting dioxy carbon to give spiroacetals **3** and **4** without the formation of other possible diastereomers **5** and **6**.[3] Because spiroacetals **3** and **4** are derived respectively from the enantiomers (*i.e.*, **1** and ***ent*-1**) of the starting racemic diols, the acetalization with *l*-menthone gives rise to a 1:1 mixture of **3** and **4**. Spiroacetals **3** and **4** can be readily separated by silica gel flash chromatography and afford enantiomerically pure diols **1** and ***ent*-1**, respectively, by their hydrolysis.

In contrast to the acetalization with *l*-menthone, reaction of the racemic diols with racemic (*dl*-) menthone proceeds diastereoselectively under thermodynamic conditions to give spiroacetal ***rac*-4** as a major product (eq 1).[4,5] The thermodynamically controlled acetalization was successfully applied to an enantioselective transformation of *meso*-1,3,5-pentanetriols **7** which possess both (*R*)- and (*S*)-1,3-diol moieties within molecules (eq 2).[4]

In connection with our recent study of an asymmetric synthesis of C(19)-C(27) segment of rifamycin S,[6] we became interested in the acetalization of 1,3-alkanediols under kinetically controlled conditions. Provided there is a significant difference in rate of the acetalization with *l*-menthone, diol **1** or ***ent*-1** can be enantioselectively converted into the corresponding spiroacetal **3** or **4**, respectively. We report here an enantioselective acetalization of racemic 1,3-alkanediols with *l*-menthone under kinetically controlled conditions and its application to kinetic resolution of the 1,3-diols.



Scheme 1



RESULTS AND DISCUSSION

The acid-catalyzed acetalization of racemic 1,3-diol ***rac*-1a** and its bis-TMS ether ***rac*-2a** with menthone was studied under a variety of conditions (eq 3, Table 1). Because spiroacetals **3a** and **4a** are derived from diols **1a** and ***ent*-1a**, respectively, their ratio is influenced by the stoichiometry of the substrates especially in their higher conversions. In order to evaluate an inherent kinetic stereoselectivity, most reactions were carried out using *dl*-menthone.[7]

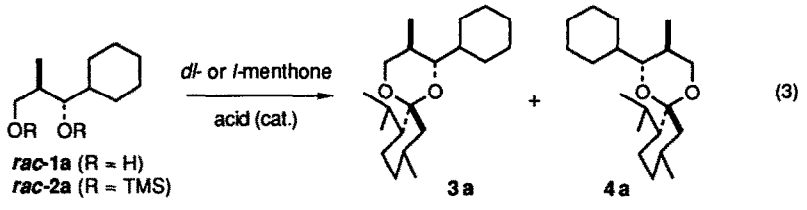


Table 1 Stereoselective Acetalization of ***rac*-1a** and ***rac*-2a** with Menthone[a]

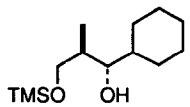
Entry	Substrate[b]	Menthone[b]	Acid[b]	Additive[b]	Time (h)	3a:4a[c]	Yield (%)
1	***rac*-2a** (1.0)	*dl*- (2.0)	TMSOTf (0.2)	-	18	1:5.4	99
2	***rac*-2a** (1.0)	*dl*- (2.0)	TfOH (0.1)	-	18	1:5.2	81
3	***rac*-2a** (1.0)	*dl*- (2.0)	TMSOTf (0.2)	-	2	1:1.6	20
4	***rac*-1a** (2.0)	*l*- (1.0)	TfOH (0.4)	-	2	3.5:1	16
5	***rac*-1a** (1.0)	*dl*- (2.0)	TfOH (0.1)	-	18	3.3:1	32
6	***rac*-1a** (2.0)	*l*- (1.0)	TfOH (0.4)	4A sieves	5	2.4:1	59
7	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (0.25)	18	1:1.8	94
8	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (0.5)	18	1:2.0	85
9	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (1.0)	18	1.8:1	89
10	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (1.5)	18	7.9:1	70
11	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (2.0)	18	8.9:1	76
12[d]	***rac*-2a** (2.0)	*dl*- (1.0)	TfOH (0.2)	H_2O (1.0)	2	11:1	59
13[d]	***rac*-2a** (2.0)	*l*- (1.0)	TfOH (0.2)	H_2O (1.0)	2.5	6.6:1	63
14[d]	***rac*-2a** (3.0)	*l*- (1.0)	TfOH (0.3)	H_2O (1.0)	2	7.5:1	58
15[d,e]	***rac*-2a** (2.0)	*l*- (1.0)	TfOH (0.2)	H_2O (1.0)	1.5	10:1	88
16[e]	***rac*-1a** (1.0)	**10** (1.0)	TfOH (0.1)	-	1.5	9.3:1	51

[a]Unless otherwise noted, all reactions were performed in CH_2Cl_2 at -40 °C under argon atmosphere. [b]The value in parenthesis indicates the equivalent of reagents (or a substrate). [c]Determined by capillary GC analysis (30 m, PEG-20M). [d]After treatment of ***rac*-2a** with 0.5 equiv of H_2O in the presence of TfOH at 0°C for 2 h, *l*-menthone was added to the resulting mixture at -40 °C. [e]Reaction was performed in THF.

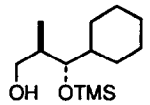
Reaction of ***rac*-2a** with *dl*-menthone in CH_2Cl_2 catalyzed either by trimethylsilyl trifluoromethanesulfonate (TMSOTf)[8] or trifluorometanesulfonic acid (TfOH) yielded an equilibrium mixture of ***rac*-3a** and ***rac*-4a** in which thermodynamically more stable[4] spiroacetal ***rac*-4a** predominated (entries 1 and 2). No selectivity was observed in the early, kinetic phase of the reaction (entry 3). Interestingly, TfOH-catalyzed condensation of diol ***rac*-1a** with *l*-menthone resulted in the preferential formation of thermodynamically less stable spiroacetal **3a** (entry 4) although the reaction did not go to completion under these conditions (entry 5). Addition of 4A sieves improved the yield but lowered the selectivity for the kinetic product **3a** probably due to the competing isomerization to the thermodynamic product **4a** (entry 6).

Although it is generally believed that acetalization reaction using bis-TMS derivatives should be performed under the strictly anhydrous conditions, we found that the acetalization ***rac*-2a** (2.0 equiv) with menthone proceeds smoothly in the presence of a small amount of water and, more importantly, that the product ratio was dramatically affected by the amounts of water (entries 7-11). Thus, in the presence of 1.0 equiv of water, TfOH-catalyzed reaction of ***rac*-2a** with *dl*-menthone gave ***rac*-3a** as a major product (1.8:1). The selectivity increased to 8.9:1 when a similar reaction was performed in the presence of 2.0 equiv of water.

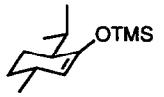
Partial hydrolysis of ***rac*-2a** with 0.5 equiv of H_2O in the presence of TfOH at 0 °C for 2 h afforded a 71:7:11:11 mixture of mono-TMS ethers **8a**, **9a**, bis-TMS ether ***rac*-2a**, and diol ***rac*-1a**. Treatment of the resulting mixture with *dl*-menthone at -40 °C for 2 h led to a smooth acetalization to afford ***rac*-3a** with high stereoselectivity (11:1, entry 12). Under similar conditions, reaction with *l*-menthone gave **3a** stereoselectively while the selectivity lowered slightly (entries 13 and 14). THF was found to be a better solvent and the reaction in this solvent gave **3a** in higher selectivity (10:1) as well as in higher yield (88%) (entry 15).



8a



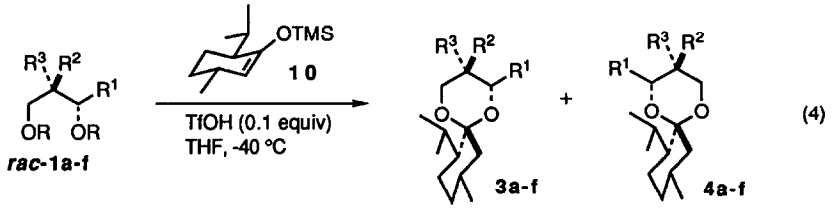
9a



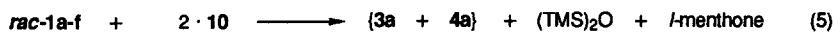
10

TMSOTf-catalyzed reaction of TMS derivatives of alcohols is known to be one of the most powerful methods for preparing acetals.[8] The efficiency of the reaction, in comparison with that of free alcohol, is accounted by irreversible formation of $(TMS)_2O$ which allows the reaction to attain completion. However, the feature does not necessarily imply that the TMS derivatives are kinetically more reactive than the free alcohols. It should be noted that the partially hydrolyzed mixture of bis-TMS ether ***rac*-2a** underwent acetalization faster than the bis-TMS ether itself (entry 3 *vs* entries 13-15). The observation suggests that free alcohols are kinetically more reactive in acetalization than the TMS derivatives. Use of more than 2.0 equiv (with respect to menthone) of the partially hydrolyzed mixture results in the formation of 1.0 equiv of $(TMS)_2O$ which is necessary for the reaction to attain completion. In the mixture, ***rac*-1a**, **8a**, **9a**, and ***rac*-2a** are in rapid equilibrium. Acetalization may, therefore, proceed with the diol and/or mono-TMS ethers.

It has been reported that isopropenyloxytrimethylsilane serves as an efficient silylating agent of alcohols and phenols in the presence of acid catalysts.[9] Analogously, acid-catalyzed reaction of diol ***rac*-1a** with 1.0 equiv of *l*-menthone enol silyl ether (**10**) may afford a mixture of the silylated derivatives and *l*-menthone, which may subsequently undergo a kinetically controlled acetalization reaction. Indeed, it was found that kinetic acetalization can be accomplished by merely treating an equimolar mixture of the diol and enol silyl ether **10** in the presence of TfOH (10 mol%) in THF (entry 16)(eq 4). Stereoselectivity was comparable to that observed in the reaction of the partially hydrolyzed bis-TMS ether. It should be noted that the reaction stopped at about 50% conversion because of the stoichiometry shown in eq 5.



(4)



(5)

A variety of 1,3-alkanediols ***rac*-1a-f** undergo kinetically controlled acetalization by treatment with enol silyl ether **10** to give thermodynamically less favorable[4] spiroacetals **3a-f** as major products in nearly 50% yields (eq 4, Table 2). Higher level of the selectivities was observed in the reaction at the lower temperatures though the longer reaction time was required under these conditions (entries 2-4). The selectivity depends considerably upon solvent used (entries 2, 5-7). The best result was obtained when THF was used. In comparison with ***rac*-1a**, other diols exhibited lower levels of the selectivity. In these reactions, the ratios (**3**:**4**) were not so high even in the lower conversion.[10] This suggests that the lower selectivity is not due to the partial isomerization of **3** to **4** but due to the lack of the inherent kinetic selectivities.

Acetalization with **10** can be utilized as a simple method for kinetic resolution of 1,3-alkanediols (Table 3). Thus, for example, reaction of ***rac*-1a** with 1.0 equiv of **10** in THF at -40 °C for 1.5 h and subsequent treatment of the resulting mixture with additional 0.5 equiv of **10** for 2 h afforded the diastereomeric spiroacetals (**3a**:**4a** = 1.8:1) and diol ***ent*-1a** in 76 and 22% yield, respectively (entry 1). Enantiomeric purity of the recovered diol was determined to be 95% ee by specific rotation measurement. Diols ***rac*-1b-f** which showed the lower kinetic selectivity than ***rac*-1a** can also be resolved by a similar procedure to give ***ent*-1b-f** of relatively high ee. The reaction should be performed by adding 1.5 equiv of **10** in two times (Method A; 1.0 + 0.5 equiv or Method B; 0.75 + 0.75 equiv) with a proper interval (1-2 h). Addition of **10** in one time (Method C) brought about nonselective formation of the diasteromeric spiroacetals (entry 4) probably due to the undesirable formation of bis-TMS ether **2**.

Table 2 Kinetically Controlled Acetalization of 1,3-Alkanediols *rac*-**1a-f** with *l*-Menthone Enol Silyl Ether **10**

Entry	Substrate	Solvent	Temp. (°C)	Time (h)	Products	3:4[a]	Yield (%)
1[b]	*rac*-**1a**; R^1 = ^{c}Hex, R^2 = Me, R^3 = H	THF	-40	1.5	**3a,4a**	9.3:1	51
2[c]	*rac*-**1b**; R^1 = Me_3CCH_2, R^2, R^3 = H	THF	-40	1.0	**3b,4b**	2.7:1	53
3	*rac*-**1b**	THF	0	0.5	**3b,4b**	1:1.2	53
4	*rac*-**1b**	THF	-60	8.0	**3b,4b**	3.5:1	50
5	*rac*-**1b**	CH_2Cl_2	-40	0.5	**3b,4b**	1:1.6	51
6	*rac*-**1b**	Et_2O	-40	2.0	**3b,4b**	2.0:1	56
7	*rac*-**1b**	CH_3CN	-40	4.0	**3b,4b**	1:1.7	60
8	*rac*-**1c**; R^1 = ^{i}Pr, R^2, R^3 = H	THF	-40	2.0	**3c,4c**	1.9:1	45
9	*rac*-**1d**; R^1 = $PhCH_2CH_2$, R^2, R^3 = H	THF	-40	1.5	**3d,4d**	1.9:1	50
10	*rac*-**1e**; R^1 = Bu, R^2 = Me, R^3 = H	THF	-40	2.5	**3e,4e**	2.3:1	53
11	*rac*-**1f**; R^1 = Bu, R^2 = H, R^3 = Me	THF	-40	1.5	**3f,4f**	2.0:1	48

[a]Determined by capillary GC analysis (30 m, PEG-20M). [b]*ent*-**1a** of 70% ee was recovered in 44% yield. [c]*ent*-**1b** of 54% ee was recovered in 44% yield.

Acid-catalyzed acetalization reaction is believed to proceed through a stepwise mechanism involving several reactive intermediates.[11,12] Moreover, mono- and non-silylated diols can participate in the present acetalization reaction. Therefore, the kinetic stereoselectivity observed in the acetalization of 1,3-alkanediols with menthone should be a result of complex factors. One of the most plausible rationalization of the observed selectivity is represented by Scheme 2. The primary hydroxy group in **1** and/or **9** is expected to undergo addition reaction to give hemiacetals **11** more rapidly than the sterically more hindered secondary hydroxy group in **1** and/or **8**. It has been reported that menthone and its oxocarbonium derivative undergo a highly stereoselective reaction with nucleophiles from the equatorial direction.[13] Intramolecular attack of the oxygen atom in the oxocarbonium ion intermediates **12** may, therefore, proceed in a diastereofacial manner from the equatorial direction to give spiroacetal **3** as a major product. On the other hand, a similar equatorial cyclization of the oxocarbenium ion in-

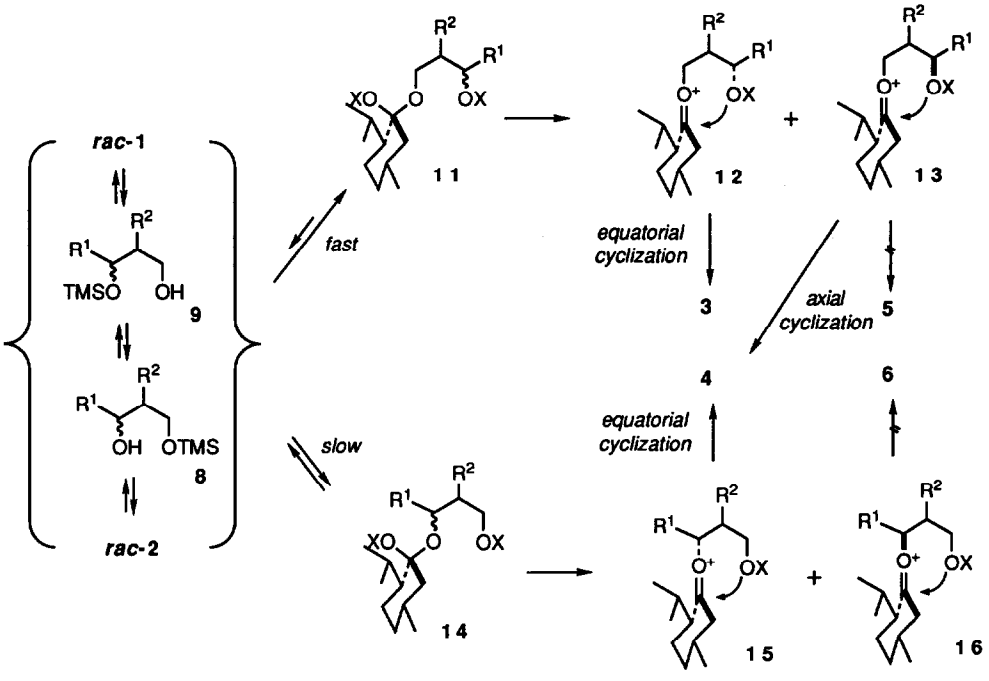
Table 3 Kinetic Resolution of 1,3-Alkanediols *rac*-**1a-d** by Acetalization with *l*-Menthone Enol Silyl Ether **10**[a]

Entry	Substrate	Method[b]	Time (h)[c]	3:4[d]	Yield (%)		Ee (%)[e]	$[\alpha]_D$ (deg)
					3+4	*ent*-**1**		
1	*rac*-**1a**	A	1.5, 2.0	1.8:1	76	22	95	+23.1 (*c* 0.59, $CHCl_3$)
2	*rac*-**1b**	A	3.5, 1.5	1.8:1	75	21	81	+13.3 (*c* 0.94, $CHCl_3$)
3	*rac*-**1b**	B	2.0, 1.0	1.9:1	67	19	75	+12.1 (*c* 1.98, $CHCl_3$)
4	*rac*-**1b**	C	3.0	1.0:1	[f]	[f]	[f]	
5	*rac*-**1c**	A	1.5, 1.0	1.4:1	72	10	71	-8.0 (*c* 1.93, $CHCl_3$)
6	*rac*-**1c**	B	1.5, 1.5	1.4:1	69	15	76	-8.6 (*c* 2.11, $CHCl_3$)
7	*rac*-**1d**	A	1.5, 1.0	1.5:1	72	29	55	-10.4 (*c* 2.26, $CHCl_3$)[g]
8	*rac*-**1d**	B	2.0, 1.5	2.0:1	61	26	55	-10.4 (*c* 1.44, $CHCl_3$)[g]
9	*rac*-**1e**	A	0.7, 0.5	1.6:1	77	20	62[h]	19.2 (*c* 2.19, $CHCl_3$)
10	*rac*-**1f**	A	1.5, 1.5	1.5:1	73	26	69[h]	5.1 (*c* 1.74, $CHCl_3$)

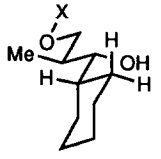
[a]All reactions were performed at -40 °C under argon atmosphere in THF. [b]Method A; 1.0, and then 0.5 equiv of **10** were added in two times. Method B; 0.75 equiv each of **10** was added in two times. Method C; 1.5 equiv of **10** was added in one time. [c]Reaction times before and after the second addition of **10** are shown in this order. [d]Determined by capillary GC analysis (30 m, PEG-20M). [e]Unless otherwise noted, determined by specific rotation measurement. [f]Not determined. [g]Measured after converting *ent*-**1d** into the corresponding bis-acetate derivatives. [h]Determined by capillary GC analysis after converting into the menthonide derivatives. See, for detail, experimental section.

termediate **13**, derived from ***ent*-1**, should be strongly prohibited because this would afford highly unstable spiroacetal **5**.[3] Minor spiroacetal **4** might be produced either through the unfavorable axial cyclization of **13** or through equatorial cyclization of **15** derived from minor secondary hemiacetal **14**.

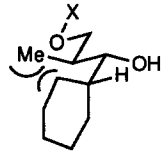
The explanation is in consistent with the observation that ***rac*-1a** showed the higher level of selectivity than the other diols. The diol exclusively adopts conformation **17** in which the secondary hydroxy group is considerably hindered. The alternative conformers such as **18** are of high energy due to the repulsive interaction between the methyl and the cyclohexyl group. On the other hand, other 1,3-diols are conformationally flexible and the differences in reactivities between the primary and the secondary hydroxy groups are less than that of ***rac*-1a**.



Scheme 2 (X = H or TMS)



17 (X = H or TMS)



18 (X = H or TMS)

EXPERIMENTAL

Unless otherwise noted, ^{1}H NMR spectra of $CDCl_3$ solution were recorded at 300 MHz. Microanalyses were performed by the Microanalysis Center of Kyoto University. GC analyses were performed with 20 m PEG-20M and 30 m OV-1 capillary columns. Wakogel C-300 was used for flash chromatography. Unless otherwise specified, all organic extracts were dried over Na_2SO_4. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 and DMF were distilled from CaH_2.

The racemic diols ***rac*-1a-d** and bis-TMS ether ***rac*-2a** were prepared as described previously.[2]

(2*S**,3*R**)-2-Methyl-1,3-heptanediol (*rac*-1e)

To a DMF (55 mL) solution of 2-methyl-2-heptene-3-ol (7.10 g, 56.4 mmol, which was prepared in 76% yield by the reaction of pentanal with $(CH_2=C(CH_3))MgBr$) at 25 °C were added successively imidazole (5.60 g, 82.2 mmol) and *t*-$BuMe_2SiCl$ (9.10 g, 60.4 mmol). The mixture was stirred for 14 h at 25 °C, and then it was diluted with hexane and was washed twice with water. The organic layer was dried and then concentrated *in vacuo*. Distillation of the residue gave 11.9 g (87%) of 3-(*tert*-butyldimethylsiloxy)-2-methylheptene: bp 91 - 91.5 °C / 7 mmHg; ^{1}H NMR δ 0.00 (3H, s), 0.03 (3H, s), 0.86-0.91 (12H, m, including s (9H) at 0.88), 1.13-1.34 (4H, m), 1.39-1.57 (2H, m), 1.66 (3H, br s), 4.00 (1H, t, *J* = 6.3), 4.73-4.74 (1H, m), 4.83 (1H, m); IR (liquid film) 3070 (s), 1655 (s), 1255 (s), 1080 (s), 895 cm^{-1} (s); mass spectrum (CI), m/z (relative intensity) 243 (M^++1, 13), 227 (10), 185 (100); exact mass calcd for $C_{14}H_{30}OSi$: 242.2067, found 242.2056.

To a THF (68 mL) suspension of 9-BBN (8.20 g, 68 mmol) at -80 °C was added a solution of the silyl ether (11.0 g, 45.3 mmol) in THF (68 mL). The mixture was stirred for 19 h during which time it was allowed to warm to rt. The mixture was cooled to -10 °C and 6 N aq NaOH (15 mL) and 30% H_2O_2 (30 mL) were successively added. The mixture was stirred for 2 h during which time it was allowed to warm to 25 °C. Brine was then added and the mixture was extracted twice with EtOAc. The combined extracts were dried and then concentrated *in vacuo* to give an oil. This was purified by flash chromatography (hexane/EtOAc, gradient elution from 95:5 to 50:50) to give 12.1 g (103%) of a 8:1 mixture of (2*S**,3*R**)- and (2*R**,3*R**)-3-(*tert*-butyldimethylsiloxy)-2-methylheptanol: ^{1}H-NMR δ 0.08 (3H, s), 0.090 (3H, s), 0.85-0.92 (12H, m, including s (9H) at 0.90), 1.00 (3H, d, *J* = 7.1), 1.23-2.78 (4H, m), 1.52-1.61 (2H, m), 1.69-1.81 (1H, m), 2.68 (1H (O*H* of minor isomer), dd, 3.8, 6.8), 2.77 (1H (O*H* of major isomer), dd, *J* = 4.4, 6.6), 3.52 (1H, ddd, *J* = 5.1, 6.3, 11.3), 3.68 (1H, dt, *J* = 4.5, 5.7), 3.80 (1H, td, *J* = 4.0, 10.9); IR (liquid film) 3350 (br), 1460 (s), 1250 (s), 1080 cm^{-1} (s).

A mixture of the siloxy alcohol (8.48 g, 32.5 mmol), concentrated HCl (20 mL), and THF (60 mL) was stirred for 18 h at a room temperature. The mixture was concentrated *in vacuo*. After drying the residue by azeotropic distillation of the solvent, the crude product was distilled under vacuum (123 °C / 8 mmHg) to give 3.79 g (80%) of a 8:1 mixture of ***rac*-1e**[14] and ***rac*-1f**.

(2*R**,3*R**)-2-Methyl-1,3-heptanediol (*rac*-1f)[15]

To a THF (20 mL) solution of thexylborane ($Me_2CHC(Me)_2BH_2$) (10 mmol) which was prepared by the reaction of 2,3-dimethyl-2-butene with BH_3-Me_2S was added a solution of 2-methyl-2-heptene-3-yl vinyl ether[16] (808 mg, 5.25 mmol) in THF (10 mL) at -80 °C. The mixture was stirred for 20 h during which time it was allowed to warm to rt. The mixture was cooled to -10 °C and 6 N aq NaOH (2 mL) and 30% H_2O_2 (4 mL) were successively added. The mixture was stirred for 2 h during which time it was allowed to warm to 25 °C. Brine was then added and the mixture was extracted twice with EtOAc. The combined extracts were dried and then concentrated *in vacuo* to give an oil. This was purified by flash chromatography (hexane/EtOAc, 50:50) to give 601 mg (78%) of ***rac*-1f**: bp 170 °C / 40 mmHg (Kugel rohr); ^{1}H-NMR δ 0.88 (3H, d, *J* = 6.9), 0.89 (3H, t, *J* = 6.4), 1.21-1.53 (6H, m), 1.70-1.82 (1H, m), 2.60-2.73 (1H, br), 2.80-3.00 (1H, br), 3.67 (2H, d, *J* = 5.4), 3.79 (1H, m), 3.77-3.81 (1H, m); IR (liquid film) 3350 (s), 1460 (s), 1380 (s), 1030 cm^{-1} (s); mass spectrum (CI), m/z (relative intensity) 147 (M^++1, 20), 129 (27), 111 (44), 87 (48), 69 (100); exact mass (CI) calcd for $C_8H_{19}O_2$ (M^++1) 147.1381, found 147. 1391.

Acetalization of Bis-TMS Ether *rac*-2a with Menthone in the Presence of H_2O

The reaction with *l*-menthone in THF (Table I, entry 12) is representative. To a solution of ***rac*-2a** (158 mg, 0.5 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added successively H_2O (4.5 μL, 0.25 mmol) and TfOH (4.4 μL, 0.05 mmol). The mixture was stirred for 1 h at 0 °C. Capillary GC analysis of the aliquot of the mixture showed that it contains mono-TMS ethers **8**, **9**, ***rac*-2a**, and ***rac*-1** (71:7:11:11). *l*-Menthone (38.5 mg, 0.25 mmol) was added to this mixture at -40 °C. The mixture was stirred further for 2.5 h at -40 °C and then the reaction was quenched by adding Et_3N (0.09 mL). The mixture was diluted with EtOAc and was washed with aq $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 99:1 to 70:30) to give, in order of elution, 48.3 mg (63%) of a 6.6:1 mixture of spiroacetals **3a**[2] and **4a**[2] and 55.0 mg (64%) of ***rac*-1a**.

Mono-TMS Ethers 8a and 9a

To a solution of ***rac*-2a** (633 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was added H_2O (25 μL, 1.4 mmol) at 0 °C and the mixture was stirred for 9 h at the same temperature. The reaction was quenched by the addition of Et_3N (0.2 mL). The mixture was diluted with EtOAc and was washed with aq $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 99:1 to 40:60) to give, in order of elution, 21.3 mg (3.1%) of ***rac*-2a**, 101.1 mg (20%) of **8a**, 17.8 mg (3.5%) of **9a**, and 229 mg (67%) of ***rac*-1a**. **8a**: ^{1}H NMR (C_6D_6) δ -0.02 (9H, s), 0.74 (3H, d, *J* = 6.9), 1.05-1.62 (9H, m), 1.68-1.83 (3H, m), 3.02 (1H (O*H*), d, *J* = 4.0), 3.24 (1H, td, *J* = 3.5, 7.0), 3.42 (1H, dd, *J* = 6.6, 9.9), 3.57 (1H, dd, *J* = 4.5, 9.9); IR (liquid film) 3450 (br), 2920 (s), 1450 (s), 1260 (s), 1080 cm^{-1} (s). **9a**: ^{1}H NMR (C_6D_6) δ 0.12 (9H, s), 0.91 (3H, d, *J* = 7.2), 0.96-1.06 (2H, m), 1.08-1.23 (3H, m), 1.38-1.50 (2H, m), 1.59-1.77 (4H, m), 1.80-1.92 (2H, m), 3.26 (1H, t, *J* = 5.4), 3.53 (1H, dd, *J* = 4.1, 10.4), 3.71 (1H, dd, *J* = 4.2, 10.5); IR (liquid film) 3400 (br), 2925 (s), 1450 (s), 1250 (s), 1090 cm^{-1} (s).

(1*R*,4*S*)-3-Trimethylsiloxy-2-*p*-menthene (10)

The enol silyl ether was prepared in 82% yield by treatment of *l*-menthone with LDA (1.2 equiv) in THF at -80 °C followed by silylation of the resulting lithium enolate with TMSCl (1.7 equiv). **10**: $[\alpha]_D^{20}$ 29.4° (*c* 0.490, $CHCl_3$); bp 92 - 93 °C / 12 mmHg; ^{1}H-NMR (C_6D_6) δ 0.14 (9H, s), 0.88 (3H, d, *J* = 7.2), 0.88 (3H, d, *J* = 7.1), 0.90 (3H, d, *J* = 7.1), 0.94-1.00 (1H, m), 1.25 (1H, ddt, *J* = 2.6, 10.3, 13.7), 1.49-1.66 (2H, m), 2.04-2.18 (2H, m), 2.33 (1H, d quint, *J* = 3.6, 7.1), 4.78 (1H, br s); IR (liquid film) 2950 (s), 1670 (s), 1255 (s), 1025 cm^{-1} (s); mass spectrum, m/z (relative intensity) 226 (M^+, 13), 211 (88), 183 (17), 73 (100); exact mass calcd for $C_{13}H_{26}OSi$: 226.1754, found 226.1751.

Kinetic Controlled Acetalization of *rac*-1a-e with *l*-Menthone Enol Ether 10

The reaction of ***rac*-1a** (Table 2, entry 1) is representative. To a THF (0.9 mL) solution of ***rac*-1a** (52.9 mg, 0.31 mmol) and **10** (69.6 mg, 0.31 mmol) at -40 °C was added TfOH (2.7 μL, 0.03 mmol). The mixture was stirred for 1.5 h at -40 °C and then the reaction was quenched by adding Et_3N (0.04 mL). The mixture was diluted with EtOAc and was washed with aq NaHCO3. The organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 99:1 to 40:60) to give, in order of elution, 48.5 mg (51%) of a 9.3:1 mixture of **3a** and **4a** and 23.4 mg (44%) of **1a** ($[\alpha]_D^{20}$ +16.9° (c 0.468, $CHCl_3$), 70% ee).

By a procedure similar to that described above, spiroacetals **3b-d**,[2] **4b-d**,[2] **3e,f**, and **4e,f** were obtained.

Spiroacetal 3e: bp 110 °C / 0.05 mmHg (Kugelrohr); ^{1}H NMR δ 0.64 (1H, t *J* = 13.2), 0.71 (3H, d, *J* = 6.9), 0.86-0.93 (12H, m), 1.20 (1H, td, *J* = 2.8, 12.0), 1.29-1.73 (12H, m), 2.37 (1H, d sept, *J* = 2.4, 7.0), 2.65 (1H, br d, *J* = 13.4), 3.38 (1H, t, *J* = 11.3), 3.53 (1H, dd, *J* = 2.6, 7.1), 3.60 (1H, dd, *J* = 5.0, 11.6); IR (liquid film) 2950 (s), 1460 (s), 1265 (s), 1125 (s), 1035 cm^{-1} (s); mass spectrum, m/z (relative intensity) 282

(M^+,10), 267 (6), 225 (15), 197 (17), 111 (41), 69 (100); exact mass calcd for $C_{18}H_{34}O_2$: 282.2560, found 282,2541. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found C, 76,67; H, 12.26.

Spiroacetal 4e: bp 110 °C / 0.05 mmHg (Kugelrohr); ^{1}H NMR δ 0.67 (1H, t, *J* = 12.9), 0.71 (3H, d, *J* = 6.7), 0.84-0.94 (12H, m), 1.18 (1H, m), 1.27-1.38 (4H, m), 1.40-1.65 (7H, m), 1.72 (1H, br d, *J* = 12.6), 2.39 (1H, d sept, *J* = 1.8, 7.0), 2.66 (1H, ddd, *J* = 2.2, 3.1, 13.2), 3.32 (1H, m), 3.61 (1H, dd, *J* = 11.3, 18.8), 3.64 (1H, d, *J* = 2.7); IR (liquid film) 2950 (s), 1460 (s), 1270 (s), 1165 (s), 1120 cm^{-1} (s); mass spectrum, m/z (relative intensity) 282 (M^+, 11), 267 (8), 225 (12), 197 (16), 111 (38), 69 (100); exact mass calcd for $C_{18}H_{34}O_2$: 282.2560, found 282.2573. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found C, 76.30; H, 12.27.

Spiroacetal 3f: bp 110 °C / 0.05 mmHg (Kugelrohr); ^{1}H NMR δ 0.63 (1H, t, *J* = 12.9), 0.88-0.94 (12H, m, including d (6H, *J* = 6.9) at 0.89 and d (3H, *J* = 6.9) at 0.93), 1.06 (3H, d, *J* = 6.9), 1.15-1.52 (12H, m), 1.71 (1H, br d, *J* = 11.4), 2.50 (1H, d sept, *J* = 1.2, 6.9), 2.76 (1H, ddd, *J* = 2.1, 3.0, 13.5), 3.56 (1H, dd, *J* = 1.2, 11.4), 3.83 (1H, m), 4.24 (1H, dd, *J* = 2.7, 11.4); IR (liquid film) 2950 (s), 1460 (s), 1270 (s), 1160 (s), 1125 (s), 1015 cm-1 (s); mass spectrum, m/z (relative intensity) 282 (M^+,12), 267 (9), 225 (18), 197 (12), 111 (40), 69 (100); exact mass calcd for $C_{18}H_{34}O_2$: 282.2560, found 282.2571. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found C, 76.32; H, 12.12.

Spiroacetal 4f: bp 110 °C / 0.05 mmHg (Kugelrohr); ^{1}H NMR δ 0.62 (1H, t, *J* = 13.0), 0.88-0.92 (12H, m), 1.04 (3H, d, *J* = 6.9), 1.15-1.54 (12H, m), 1.70 (1H, br d, J = 10.8), 2.50 (1H, d sept, *J* = 1.8, 7.1), 2.75 (1H, ddd, *J* = 2.0, 3.0, 13.5), 3.52 (1H, dd, *J* = 1.2, 11.4), 3.95-4.05 (2H, m, including dd (1H, *J* = 2.9, 11.4) at 4.01); IR (liquid film) 2950 (s), 1460 (s), 1270 (s), 1170 (s), 1125 (s), 1015 cm^{-1} (s); mass spectrum, m/z (relative intensity) 282 (M^+, 12), 267 (9), 225 (18), 197 (13), 111 (38), 69 (100); exact mass calcd for $C_{18}H_{34}O_2$: 282.2560, found 282,2567. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found C, 76,57; H, 12.27.

Kinetic Resolution of 1,3-Alkanediols by Acetalization with *l*-Menthone

The reaction of ***rac*-1d** (Table 3, entry 7) is representative. To a THF (7.5 mL) solution of ***rac*-1d** (451 mg, 2.50 mmol) and **10** (293 mg, 1.25 mmol) at -40 °C was added TfOH (22.1 μL, 0.25 mmol). The mixture was stirred for 1.5 h at -40 °C. To the resulting mixture was added **10** (147 mg, 0.63 mmol) and stirred further for 1 h at the same temperature. The reaction was quenched by adding Et_3N (0.04 mL). The mixture was diluted with EtOAc and was washed with aq $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 99:1 to 40:60) to give, in order of elution, 566 mg (72%) of a 1.5:1 mixture of **3d** and **4d** and 128 mg (29%) of ***ent*-1d.** Optical purity of the diols was determined after converting into the bis-acetate derivative (Ac_2O, 4-(*N*,*N*-dimethylamino)pyridine, pyridine, 100% yield) (55% ee, $[\alpha]_D^{20}$ -10.4° (*c* 2.26, $CHCl_3$).

By a procedure similar to that described, ***ent*-1a-f** were obtained. Optical purities of ***ent*-1a-d** were determined by specific rotation measurements based on their maximum rotations reported previously.[2] Optical purities of ***ent*-1e** and ***ent*-1f** were determinded by converting them into the menthonide derivatives. Thus, ***ent*-1e** (15.9 mg, 0.11 mmol) was treated with **10** (0.33 mmol) in the presence of TfOH (1 μL) in CH_2Cl_2 (0.33 mL) at -40 °C for 24 h. The usual work-up followed by purification by flash chromatography gave a 4.31:1 mixture of **4a** and **3a** in 92% yield. A similar reaction of ***ent*-1f** gave a 5.52:1 mixture of **4f** and **3f** in 85% yield.

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